Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 9758–9763

An organo-catalytic approach to the enantioselective synthesis of (*R*)-selegiline

Siva Kumar Talluri and Arumugam Sudalai*

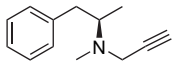
Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411 008, India

Received 2 March 2007; revised 19 June 2007; accepted 6 July 2007
Available online 13 July 2007

Abstract—An efficient enantioselective synthesis of (*R*)-selegiline has been achieved by two routes, via proline-catalyzed α-aminooxylation as well as α-amination of phenylpropanaldehyde as the key step.

1. Introduction

N-Methyl-*N*-((*R*)-1-phenylpropan-2-yl)prop-2-yn-1-amine (**1**) (Selegiline), a levorotatory acetylenic derivative of phenethylamine is commonly referred to in the clinical and pharmacological literature as L-deprenyl. It is a selective, irreversible inhibitor of monoamineoxidase-B (MOA) and is quite effective in the treatment of Parkinson's disease as well as Alzheimer's disease[1] when used along with L-DOPA. Selegiline (**1**) has been reported to retard the further deterioration of cognitive functions to more advanced milestones in Alzheimer's disease.[2] The propargylamine pharmacophore of selegiline (**1**) and related compounds also appears to have neuroprotective activity independent of MAO inhibition.[3] All these biological properties make selegiline (**1**) a very attractive synthetic target. Even though several methods are available for the synthesis of racemic selegiline,[4] scant attention[5] has been given to the enantioselective synthesis of (*R*)-selegiline (**1**).



(*R*)-Selegiline **1**

All the methods for the synthesis of (*R*)-selegiline (**1**) make use of either (*R*)-deoxyephedrine, or L-phenyl alanine as the starting material, or classical resolution of amines using D-tartaric acid. Recently, we have reported the synthesis of (*R*)-selegiline (**1**) using OsO_4-catalyzed asymmetric dihydroxylation.[6] All these methods suffer from the fact that they involve resolution of racemic selegiline where half of the material is lost, or involve use of a toxic osmium catalyst. In this context, a process for its direct production of the pure enantiomer from a prochiral substrate is highly desirable. As a part of our research program aimed at developing stereocontrolled synthesis of bioactive molecules,[7] herein we report a short and effective procedure for the synthesis of (*R*)-selegiline (**1**) in high enantiomeric purity using proline-catalyzed α-aminooxylation and α-amination of commercially available 3-phenylpropanaldehyde (**2**).

2. Result and discussion

The field of asymmetric organocatalysis is rapidly developing and attracts an increasing number of research groups around the world. In particular, organo-catalytic asymmetric syntheses have provided several new methods for obtaining chiral compounds in an efficient manner.[8] In this context, proline, an abundant, inexpensive amino acid available in both enantiomeric forms, has emerged as arguably the most practical and versatile organocatalyst.[9] Proline has also been found to be an excellent asymmetric catalyst for α-functionalization[10,11] of carbonyl compounds. In this paper we describe the enantioselective synthesis of (*R*)-selegiline (**1**) by two routes employing proline-catalyzed α-aminooxylation[10] and α-amination[11] of 3-phenylpropanaldehyde (**2**).

Firstly, α-aminooxylation[10e] of 3-phenylpropanaldehyde (**2**) was carried out using nitrosobenzene and L-proline (10 mol %) at 25 °C to furnish an aminooxy aldehyde in situ, which on reduction with $NaBH_4$ afforded the α-aminooxy alcohol **3**. Aminooxy alcohol **3** was then reduced to the corresponding diol **4** in 88% yield using hydrogenation conditions (H_2 (1 atm), 10% Pd/C, MeOH, 12 h). The diol **4** was activated as its primary tosylate and then converted in to the

Keywords: Asymmetric reactions; Organocatalysis; Proline; α-Aminooxylation; α-Amination.
* Corresponding author. Tel.: +91 20 25902174; fax: +91 20 25902676; e-mail: a.sudalai@ncl.res.in

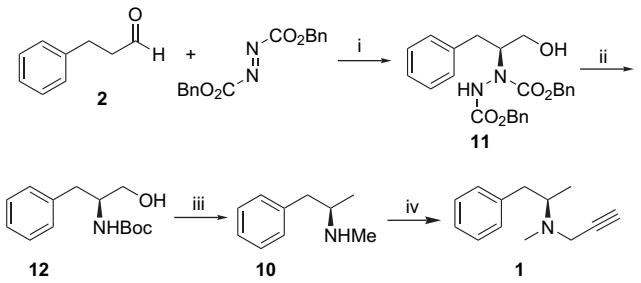
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.07.012

corresponding epoxide **5** on treatment with NaH. The epoxide **5** was then subjected to selective reductive ring opening at the terminal position with $LiAlH_4$ to give the secondary alcohol **6** in very good yield (92%). The optical purity of the alcohol **6** was determined from ^1H NMR spectroscopic analysis of its Mosher ester, which showed the enantiomeric excess to be 99%. The alcohol **6** was then converted to *N*-methylamine **10** in a four-step reaction sequence: (i) mesylation of alcohol **6** and treatment with NaN_3 to give the corresponding azide **7**; (ii) reduction of azide **7** to amine **8** (H_2 (1 atm), 10% Pd/C, MeOH, 2 h, 98%); (iii) protection of amine **8** with $(Boc)_2O$ to give *N*-Boc protected amine **9**; (iv) reduction of *N*-Boc group in **9** using $LiAlH_4$ to give *N*-methylamine **10**. Propargylation of amine **10** using propargyl bromide furnished (*R*)-selegiline (**1**) in 26% overall yield and 99% ee; $[\alpha]_D^{25}$ −10.7 (*c* 6.5, EtOH); {lit.[12] $[\alpha]_D^{25}$ −10.8 (*c* 6.4, EtOH)}.

The synthesis of (*R*)-selegiline (**1**) using α-amination (List's protocol)[11a] not only reduces the total number of steps (increase the overall yield) but also rules out the inversion of the chiral center, which is required in the α-aminooxylation approach. Thus, 3-phenylpropanaldehyde (**2**) was reacted with dibenzyl azodicarboxylate in the presence of D-proline (10 mol %) to give an aminoaldehyde, which on reduction with $NaBH_4$ afforded the protected amino alcohol **11** in 95% yield and 95% ee.[11a] The amino alcohol **11** was then hydrogenated using Raney-nickel as catalyst to give aminoalcohol, which was converted to the corresponding carbamate **12** using $(Boc)_2O$. The primary alcohol was then tosylted (*p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h), which on reduction with $LiAlH_4$ gave the methylamine **10** in 81% yield and 95% ee; $[\alpha]_D^{25}$ −10.36 (*c* 4.0, EtOH); {lit.[13] $[\alpha]_D^{21}$ −10.9 (*c* 4.2, EtOH)}. The secondary amine was propargylated using propargyl bromide under standard conditions to give (*R*)-selegiline (**1**) in 37% overall yield; $[\alpha]_D^{25}$ −10.28 (*c* 6.5, EtOH); {lit.[12] $[\alpha]_D^{25}$ −10.8 (*c* 6.4, EtOH)} (Schemes 1 and 2).

3. Conclusion

In conclusion, we have successfully applied proline-catalyzed α-aminooxylation and α-amination strategies toward the synthesis of (*R*)-selegiline (**1**). The reactions are rapid, and require a relatively low amount of an inexpensive and nontoxic proline-catalyst that is available in both enantiomeric forms. The high overall yields (26% via α-aminooxylation and 37% via α-amination) and the reduced number of steps render our approach a good alternative to the known methods.



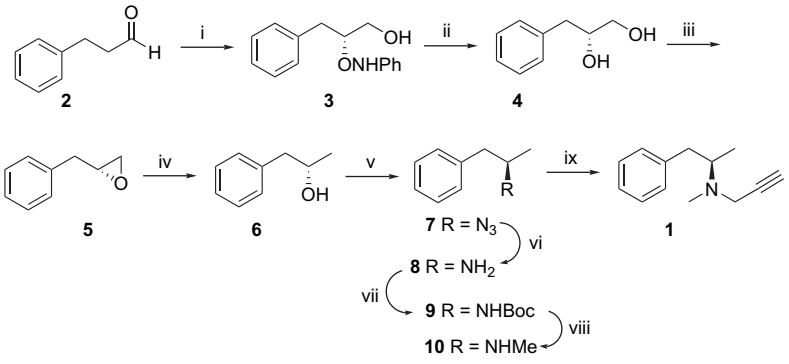
Scheme 2. Reagents and conditions: (i) dibenzyl azodicarboxylate, D-proline (10 mol %), 0–20 °C, 3 h then $NaBH_4$, EtOH, 95%; (ii) (a) H_2 (60 psi), Raney-Nickel, MeOH, AcOH, 16 h, (b) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 66% for two steps; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 2 h, (b) $LiAlH_4$, THF, reflux, 4 h, 81% for two steps; (iv) propargylbromide, K_2CO_3, CH_3CN, 12 h, 72%.

4. Experimental section

4.1. General information

Solvents were purified and dried by standard procedures before use. Melting points were uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer. Elemental analysis was carried out on a Carlo Erba CHNS-O analyzer.

4.1.1. (2*R*)-3-Phenyl-2-(*N*-phenylaminooxy)propan-1-ol (3). To a stirred solution of 3-phenylpropanaldehyde (**2**) (3.35 g, 25 mmol) and nitrosobenzene (2.25 g, 21 mmol) in DMSO (30 mL) was added L-proline (483 mg, 4.2 mmol, 20 mol %) in one portion at 25 °C. After 2 h, the temperature was lowered to 0 °C, followed by dilution with anhyd MeOH (20 mL) and careful addition of excess $NaBH_4$ (1.44 g, 38 mmol). The reaction was quenched after 10 min by pouring the reaction mixture into a vigorously stirred biphasic solution of Et_2O and aqueous HCl (1 M). The organic layer was separated, and the aqueous phase was extracted with



Scheme 1. Reagents and conditions: (i) PhNO, L-proline (10 mol %), DMSO, 25 °C, 20 min then MeOH, $NaBH_4$, 86%; (ii) H_2 (1 atm), 10% Pd/C, MeOH, 12 h, 88%; (iii) (a) *p*-TsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, (b) NaH, DMF, 0 °C, 0.5 h, 81% for two steps; (iv) $LiAlH_4$, THF, reflux, 2 h, 92%; (v) (a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 0.5 h, (b) NaN_3, DMF, 80 °C, 12 h, 76% for two steps; (vi) H_2 (1 atm), 10% Pd/C, MeOH, 2 h, 98%; (vii) $(Boc)_2O$, Et_3N, 0 °C, 1 h, 95%; (viii) $LiAlH_4$, THF, reflux, 4 h, 90%; (ix) propargyl bromide, anhyd K_2CO_3, CH_3CN, 12 h, 72%.

EtOAc (3×100 mL). The combined organic phases were dried over anhyd Na_2SO_4, concentrated, and purified by column chromatography over silica gel using EtOAc/Pet. ether (40:60) as eluant to give pure aminooxy alcohol **3**.

Yield: 4.4 g (86%); gum; $[\alpha]_D^{25}$ +42.08 (*c* 1.0, $CHCl_3$); {lit.[10e] $[\alpha]_D^{25}$ +42.1 (*c* 0.9, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): 700, 736, 908, 1029, 1070, 1265, 1454, 1494, 1600, 2925, 3028, 3060, 3280, 3404; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.84 (dd, *J*=13.6, 6.6 Hz, 1H), 3.02 (dd, *J*=13.6, 6.3 Hz, 1H), 3.71 (dd, *J*=12.3, 6.3 Hz, 1H), 3.86 (dd, *J*=12.1, 3.0 Hz, 1H), 4.09 (m, 1H), 6.82 (d, *J*=8.4 Hz, 2H), 6.92 (t, *J*=7.0 Hz, 1H), 7.13–7.31 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 36.6, 64.4, 84.9, 114.5, 122.3, 126.5, 128.3, 128.7, 129.3, 137.6, 148.0. Analysis: $C_{15}H_{17}NO_2$ requires C, 74.05; H, 7.04; N, 5.76%; found C, 74.19; H, 6.95; N, 5.70%.

4.1.2. (*R*)-3-Phenylpropane-1,2-diol (4). The aminooxy alcohol **3** (1.22 g, 5 mmol) was dissolved in methanol (15 mL) and to the solution was added 10% Pd/C (20 mg) and the reaction mixture was stirred in a hydrogen atmosphere (1 atm, balloon pressure) for 12 h. After completion of the reaction (monitored by TLC) the reaction mixture was filtered through a Celite pad, concentrated, and the crude product was then purified by silica gel chromatography using EtOAc/Pet. ether (30:70) as eluant to give pure diol **4**.

Yield: 0.67 g (88%); colorless solid; mp: 46–48 °C, {lit.[14] mp: 46–47 °C}; $[\alpha]_D^{25}$ +35.1 (*c* 1, EtOH); {lit.[14] $[\alpha]_D^{18}$ +35.4 (*c* 1, EtOH)}; IR ($CHCl_3$, cm^{-1}): 557, 657, 700, 750, 771, 858, 1031, 1089, 1176, 1218, 1456, 1602, 2860, 3026, 3392; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.35 (br s, 1H), 2.72 (d, *J*=6.3 Hz, 2H), 3.44 (dd, *J*=11.2, 7.2 Hz, 1H), 3.62 (dd, *J*=11.0, 1.8 Hz, 1H), 3.85–3.89 (m, 1H), 7.17–7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 39.7, 65.7, 73.1, 126.4, 128.4, 129.3, 138.0. Analysis: $C_9H_{12}O_2$ requires C, 71.03; H, 7.95%; found C, 71.15; H, 7.84%.

4.1.3. (*R*)-(2,3-Epoxypropyl)benzene (5). To a stirred solution of (*R*)-3-phenylpropane-1,2-diol **4** (457 mg, 3 mmol) and triethylamine (460 μL, 3.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *p*-toluenesulfonyl chloride (572 mg, 3 mmol). After stirring at 0 °C for 1 h, the mixture was poured into ice water (30 mL), washed with 20% H_2SO_4, saturated aqueous $NaHCO_3$, and brine, and dried over anhyd Na_2SO_4 to give the crude tosylate. This was then dissolved in DMF (10 mL) followed by the addition of sodium hydride (60% oil dispersion, 120 mg, 3 mmol) at 0 °C. After completion (monitored by TLC) the reaction mixture was quenched by the addition of water and the aqueous layer was extracted with Et_2O (3×30 mL). The combined organic layers were dried over anhyd Na_2SO_4, the solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluant to give pure epoxide **5**.

Yield: 0.33 g (81% for two steps); colorless liquid; $[\alpha]_D^{25}$ +17.6 (*c* 1.9, EtOH); {lit.[15] $[\alpha]_D^{25}$ +17.5 (*c* 1.94, EtOH)}; IR ($CHCl_3$, cm^{-1}): 698, 736, 847, 968, 1030, 1132, 1259, 1456, 1506, 1652, 2854, 2920; ^1H NMR (200 MHz, $CDCl_3$) δ: 2.55 (dd, *J*=5.1, 2.7 Hz, 1H), 2.75–2.90 (m, 3H), 3.11–3.20 (m, 1H), 7.24–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 38.7, 46.6, 52.3, 126.6, 128.5, 128.9, 137.1. Analysis: $C_9H_{10}O$ requires C, 80.56; H, 7.51%; found C, 80.67; H, 7.55%.

4.1.4. (*S*)-1-Phenylpropan-2-ol (6). To a stirred suspension of $LiAlH_4$ (137 mg, 3.6 mmol) in THF (10 mL) was added dropwise a solution of (*R*)-(2,3-epoxypropyl)benzene (**5**) (402 mg, 3 mmol) in THF (5 mL) at 0 °C. The reaction mixture was refluxed for 2 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by addition of EtOAc. The reaction mixture was treated with 20% NaOH (2 mL), the white precipitate formed was filtered off and the residue was washed with EtOAc (3×30 mL). The combined EtOAc layers were dried over anhyd Na_2SO_4, the solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (10:90) as eluant to give the corresponding alcohol **6**.

Yield: 0.38 g (92%); colorless liquid; $[\alpha]_D^{25}$ +50.8 (*c* 1.1, $CHCl_3$); {lit.[16] $[\alpha]_D$ +39.7 (*c* 0.515, $CHCl_3$)}; IR ($CHCl_3$, cm^{-1}): 742, 771, 941, 1032, 1080, 1121, 1219, 1339, 1458, 1541, 1652, 2930, 2968, 3031, 3296; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.2 (d, *J*=6.2 Hz, 3H), 2.0 (br s, 1H), 2.7 (m, 2H), 3.88–4.04 (m, 1H), 7.15–7.28 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 22.4, 45.5, 68.5, 126.0, 128.1, 129.2, 138.5. Analysis: $C_9H_{12}O$ requires C, 79.37; H, 8.88%; found C, 79.24; H, 8.97%.

4.1.5. Mosher's ester of 6. To a stirred solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC) (44 mg, 0.21 mmol) and 4-dimethylaminopyridine (2 mg) in CH_2Cl_2 (2 mL) at 0 °C under an argon atmosphere was added dropwise a solution of alcohol **6** (25 mg, 0.18 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 10 min and (*R*)-α-methoxy-α-trifluoromethylphenyl acetic acid (46 mg, 0.196 mmol) in CH_2Cl_2 (2 mL) was added dropwise followed by stirring at 0 °C for 1 h and then at 25 °C for 12 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with saturated aqueous $NaHCO_3$ solution (50 mL), dried over anhyd Na_2SO_4, and concentrated under reduced pressure to give Mosher ester of the alcohol **6**.

Yield: 55 mg (87%); gum; $[\alpha]_D^{25}$ +137.58 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 650, 735, 911, 957, 1015, 1122, 1217, 1242, 1348, 1495, 1519, 1606, 1753, 2850, 2927, 2952, 3158; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.36 (d, *J*=6.3 Hz, 3H), 2.79 (dd, *J*=13.9, 5.9 Hz, 1H), 2.95 (dd, *J*=13.9, 7.2 Hz, 1H), 3.46 (s, 3H), 5.39 (sextet, *J*=6.4 Hz, 1H), 7.06–7.43 (m, 10H).

4.1.6. 1-((*R*)-2-Azidopropyl)benzene (7). To a stirred solution of (*S*)-1-phenylpropan-2-ol (**6**) (408 mg, 3 mmol) and triethylamine (460 μL, 3.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfonyl chloride (232 μL, 3 mmol) dropwise via syringe. After stirring at 0 °C for 0.5 h, the mixture was poured into ice water (30 mL), washed with 20% H_2SO_4, saturated aqueous $NaHCO_3$, and brine, and dried over anhyd Na_2SO_4 to give the crude mesylate, which was dissolved in DMF (10 mL) followed by the addition of sodium azide (195 mg, 3 mmol). The reaction mixture was then heated at 80 °C for 6 h and then quenched by addition of water. The aqueous layer was extracted with Et_2O (3×30 mL) and the combined organic layers were dried over anhyd Na_2SO_4,

the solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (5:95) as eluant to yield pure azide **7**.

Yield: 0.37 g (76% for two steps); gum; $[\alpha]_D^{25}$ −49.5 (*c* 1.24, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 700, 744, 771, 873, 914, 1032, 1124, 1259, 1456, 1602, 2112, 2858, 2933, 3031; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.25 (d, *J*=6.6 Hz, 3H), 2.69 (dd, *J*=13.6, 6.7 Hz, 1H), 2.83 (dd, *J*=13.7, 7.0 Hz, 1H), 3.66 (sextet, *J*=6.7 Hz, 1H), 7.14–7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.9, 42.4, 58.8, 126.6, 128.4, 129.2, 137.6. Analysis: $C_9H_{11}N_3$ requires C, 67.06; H, 6.88; N, 26.07%; found 67.01; H, 6.84; N, 26.15%.

4.1.7. (*R*)-1-Phenylpropan-2-amine (8). 1-((*R*)-2-Azidopropyl)benzene (**7**) (483 mg, 3 mmol) was dissolved in methanol (10 mL) and Pd/C (20 mg) was added to it under hydrogen atmosphere (1 atm, balloon pressure). The mixture was stirred for 2 h and the reaction mixture was filtered through a pad of Celite and the solvent was distilled off under reduced pressure to give 0.4 g (98%) of pure (*R*)-1-phenylpropan-2-amine (**8**).

Yield: 0.4 g (98%); gum; $[\alpha]_D^{25}$ −30.3 (*c* 2.0, MeOH); {lit.[13] $[\alpha]_D$ −30.2 (*c* 2.55, MeOH)}; IR ($CHCl_3$, cm^{-1}): 700, 750, 810, 870, 1090, 1100, 1195, 1400, 1435, 1505, 1650, 2995, 3010, 3055, 3415; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.23 (d, *J*=6.1 Hz, 3H), 1.77 (br s, 2H), 2.68 (dd, *J*=13.6, 8.0 Hz, 1H), 2.78 (dd, *J*=13.5, 6.1 Hz, 1H), 3.95–4.05 (m, 1H), 7.18–7.34 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 18.3, 41.7, 50.4, 128.4, 129.9, 130.5, 137.3. Analysis: $C_9H_{13}N$ requires C, 79.95; H, 9.68; N, 10.36%; found C, 80.06; H, 9.62; N, 10.31%.

4.1.8. *tert*-Butyl (*R*)-1-phenylpropan-2-ylcarbamate (9). To a stirred solution of amine **8** (406 mg, 3 mmol) in CH_2Cl_2 (20 mL) were added triethylamine (460 μL, 3.3 mmol) and $(Boc)_2O$ (654 mg, 3 mmol) at 0 °C. After 1 h the reaction mixture was quenched by addition of water (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried over anhyd Na_2SO_4, the solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (15:85) as eluant to give pure carbamate **9**.

Yield: 0.67 g (95%); gum; $[\alpha]_D^{25}$ +7.62 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}): 700, 771, 876, 941, 1061, 1173, 1250, 1366, 1456, 1508, 1703, 2852, 2935, 2978, 3360; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.08 (d, *J*=6.7 Hz, 3H), 1.42 (s, 9H), 2.64 (dd, *J*=13.3, 7.3 Hz, 1H), 2.84 (dd, *J*=13.4, 5.6 Hz, 1H), 3.82–3.92 (m, 1H), 4.37 (br s, 1H), 7.14–7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.1, 28.4, 43.0, 47.41, 78.9, 126.2, 128.2, 129.4, 138.2, 155.0. Analysis: $C_{14}H_{21}NO_2$ requires C, 71.46; H, 8.99; N, 5.95%; found C, 71.5; H, 8.97; N, 5.91%.

4.1.9. (*S*)-2-Amino-*N*,*N*-dibenzyloxycarbonylhydrazino-3-phenylpropan-1-ol (11). To a stirred mixture containing dibenzyl azodicarboxylate (660 mg, 90%, 2 mmol) and (*S*)-proline (24 mg, 0.1 mmol) in CH_3CN (20 mL) at 0 °C, 3-phenylpropanaldehyde (**2**) (402 mg, 3 mmol) was added and stirred for 2 h. The reaction mixture was warmed to 20 °C within 1 h during, which time it became colorless. It was then cooled to 0 °C, treated with ethanol (20 mL) and $NaBH_4$ (80 mg), and stirred for 5 min at 0 °C. The reaction mixture was then quenched by the addition of aqueous NH_4Cl and extracted with EtOAc (3×30 mL). The combined organic layers were dried over anhyd Na_2SO_4, solvent was distilled off under reduced pressure and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (30:70) as eluant to yield the amino alcohol **11** in 95% yield.

Yield: 1.24 g (95%); mp: 38–40 °C; $[\alpha]_D^{25}$ +29.86 (*c* 0.4, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ: 2.65 (m, 2H), 3.57 (m, 2H), 3.90–4.30 (m, 1H), 4.50–5.00 (m, 1H), 5.00–5.40 (m, 4H), 6.40 (s, 1H), 7.00–7.60 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 33.80, 67.81, 68.2, 68.15, 68.28, 127.25, 128.38, 128.46, 128.71, 129.12, 135.25, 135.78. Analysis: $C_{25}H_{26}N_2O_5$ requires C, 69.11; H, 6.03; N, 6.45%; found C, 69.07; H, 6.06; N, 6.41%.

4.1.10. *tert*-Butyl (*S*)-1-hydroxy-3-phenylpropan-2-ylcarbamate (12). Aminoalcohol **11** (270 mg, 0.62 mmol) was added to a stirred slurry of Raney-Nickel (300 mg, pre-washed with dry methanol) in dry methanol (10 mL) and AcOH (12 drops). The mixture was hydrogenated (H_2 60 Psi) in a Parr shaker for 16 h at 20 °C, filtered over Celite, and the solvent was evaporated in a rotavapour to give the crude product (66 mg, 70%), which was dissolved in CH_2Cl_2 (10 mL) followed by the addition of triethylamine (139 μL, 1 mmol) and $(Boc)_2O$ (136 mg, 0.62 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then quenched by addition of 10% $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over anhyd Na_2SO_4, solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether (25:75) as eluant to give pure *N*-Boc protected amino alcohol **12**.

Yield: 0.1 g (66% for two steps); mp: 96–98 °C; $[\alpha]_D^{25}$ −26.6 (*c* 1.0, MeOH), {lit.[13] $[\alpha]_D^{20}$ −27 (*c* 1.0, MeOH)}; IR ($CHCl_3$, cm^{-1}): 775, 885, 1007, 1168, 1269, 1316, 1456, 1526, 1684, 2925, 2980, 3356; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 2.84 (d, *J*=7.1 Hz, 2H), 3.53 (dd, *J*=11.1, 5.3 Hz, 1H), 3.64 (dd, *J*=11.1, 3.9 Hz, 1H), 3.84 (br s, 1H), 4.9 (br s, 1H), 7.19–7.29 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 28.19, 37.33, 53.49, 63.43, 79.39, 126.19, 128.27, 129.19, 137.94, 156.01. Analysis: $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57%; found C, 66.97; H, 8.37; N, 5.51%.

4.1.11. (*R*)-*N*-Methyl-1-phenylpropan-2-amine (10). (1) *α-Aminooxylation approach*: to a stirred suspension of $LiAlH_4$ (76 mg, 2 mmol) in THF (5 mL) was added dropwise a solution of *tert*-butyl (*R*)-1-phenylpropan-2-ylcarbamate (**9**) (235 mg, 1 mmol) in THF (2 mL) at 0 °C. The reaction mixture was refluxed for 4 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by addition of EtOAc. The reaction mixture was treated with 20% NaOH (0.5 mL), the white precipitate formed was filtered off and the residue was washed with EtOAc (3×10 mL). The combined EtOAc layers were dried over anhyd Na_2SO_4, solvent

was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using $CHCl_3$ as eluant to yield the corresponding pure *N*-methyl amine **10**.

Yield: 137 mg (92%); gum; $[\alpha]_D^{25}$ −10.87 (*c* 1.0, EtOH); {lit.[13] $[\alpha]_D^{21}$ −10.9 (*c* 4.2, EtOH)}; IR ($CHCl_3$, cm^{-1}): 771, 878, 1036, 1130, 1219, 1344, 1458, 1541, 1651, 2829, 2928, 3252; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.07 (d, *J*=6.1 Hz, 3H), 2.38 (s, 3H), 2.52–2.85 (m, 3H), 7.16–7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 19.2, 33.4, 43.0, 56.1, 126.0, 128.2, 129.0, 139.0; Mass (*m*/*z*, % rel intensity): 149 (M+, 4), 134 (10), 119 (5), 117 (5), 91 (45), 65 (16), 58 (100). Analysis: $C_{10}H_{15}N$ requires C, 80.49; H, 10.12; N, 9.38%; found C, 80.41; H, 10.12; N, 9.45%.

(2) *α-Amination approach*: to a stirred solution of *N*-Boc protected amino alcohol **12** (251 mg, 1 mmol) in CH_2Cl_2 (5 mL) were added triethylamine (153 μL, 1.1 mmol) and *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then quenched by addition of 10% $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over anhyd Na_2SO_4, concentrated on rotavapour to give the crude tosylate, which dissolved in THF (5 mL), and added dropwise to a suspension of $LiAlH_4$ (114 mg, 3 mmol) in THF (20 mL). The reaction mixture was refluxed for 4 h and then cooled to 0 °C and the excess $LiAlH_4$ was quenched by addition of EtOAc. The reaction mixture was treated with 20% NaOH (0.5 mL), the white precipitate formed was filtered off, and the residue was washed with EtOAc (3×10 mL). The combined EtOAc layers were dried over anhyd Na_2SO_4, solvent was distilled off under reduced pressure, and the crude product was purified by column chromatography over silica gel using $CHCl_3$ as eluant to yield the corresponding pure *N*-methyl amine **10**; $[\alpha]_D^{25}$ −10.36 (*c* 4.0, EtOH); {lit.[13] $[\alpha]_D^{21}$ −10.9 (*c* 4.2, EtOH)}.

4.1.12. *N*-Methyl-*N*-((*R*)-1-phenylpropan-2-yl)prop-2-yn-1-amine: (*R*)-selegiline (1). (1) *α-Aminooxylation approach*: to a stirred solution of (*R*)-2-(methylamino)-1-phenylpropane (**10**) (200 mg, 1.34 mmol) in CH_3CN (10 mL) were added anhyd K_2CO_3 (277 mg, 2.01 mmol) and propargyl bromide (478 mg, 4.02 mmol). The reaction mixture was then stirred for 12 h at 25 °C, the solid residue formed was then filtered off, and the solvent was distilled off under reduced pressure to give the crude product, which was purified by column chromatography over silica gel using $CHCl_3$ as eluant to give pure (*R*)-selegiline **1**.

Yield: 0.18 g (72%); gum; $[\alpha]_D^{25}$ −10.7 (*c* 6.5, EtOH); {lit.[12] $[\alpha]_D^{25}$ −10.8 (*c* 6.4, EtOH)}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.95 (d, *J*=6.0 Hz, 3H), 2.25 (t, *J*=2.0 Hz, 1H), 2.35 (s, 3H), 2.40–2.55 (m, 1H), 2.80–3.10 (m, 2H), 3.40 (d, *J*=2.0 Hz, 2H), 7.00–7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.1, 31.4, 46.8, 51.9, 60.8, 68.1, 82.2, 125.6, 128.3, 128.6, 140.2. Analysis: $C_{13}H_{17}N$ requires C, 83.37; H, 9.14; N, 7.47%; found C, 83.34; H, 9.11; N, 7.53%.

(2) *α-Amination approach*: $[\alpha]_D^{25}$ −10.28 (*c* 6.5, EtOH); {lit.[12] $[\alpha]_D^{25}$ −10.8 (*c* 6.4, EtOH)}.

Acknowledgements

S.K.T. thanks CSIR, New Delhi, for financial support. The authors thank Dr. B. D. Kulkarni, Head, CE-PD Division, for his constant encouragement and support.

References and notes

1. (a) Mizutta, I.; Ohta, M.; Ohta, K.; Nishimura, M.; Mizutta, E.; Hayashi, K.; Kuna, S. *Biochem. Biophys. Res. Commun.* **2000**, *279*, 751; (b) Vaglini, F.; Pardini, C.; Cavalletti, M.; Maggio, R.; Corsini, G. U. *Brain Res.* **1996**, *741*, 68.
2. Sano, M.; Ernesto, C.; Thomas, R. C.; Klauber, M. R. *N. Engl. J. Med.* **1997**, *336*, 1216.
3. (a) Abu-Raya, S.; Blaugrund, S.; Tremblower, V.; Shilderman, E.; Shohami, E. *J. Neurosci. Res.* **1999**, *58*, 456; (b) Paterson, I. A.; Tatton, W. G. *Adv. Pharmacol.* **1998**, *42*, 312.
4. (a) Flower, J. S. *J. Org. Chem.* **1977**, *42*, 2637; (b) Gyogy, B.; Jozsef, K.; Eva, S.; Sandor, V.; Ferenc, Z. *Chem. Abstr.* **1988**, *110*, 44960; (c) Plenevaux, A.; Flower, S. F.; Dewey, S. L.; Wolf, A. P.; Guillaume, M. *Appl. Radiat. Isot.* **1991**, *42*, 121.
5. (a) Josef, H.; Jiri, H.; Pavel, P.; Bohumila, B.; Milan, F.; Jiri, K.; Lubomir, K.; Josef, P. *Chem. Abstr.* **1989**, *113*, 5900; (b) Josef, H.; Jiri, H.; Pavel, P.; Bohumila, B.; Milan, F.; Jiri, K.; Lubomir, K.; Josef, P. *Chem. Abstr.* **1991**, *117*, 150680; (c) Silvia, O.; Richard, C.; Jeorg, S.; Hans, W. *Chem. Abstr.* **1996**, *124*, 288969x; (d) Sterling, J.; Herzig, Y.; Goren, T.; Finkelstein; Lerner, D.; Goldenberg, W.; Miskolezi, I.; Molnar; Rantal, F. *J. Med. Chem.* **2002**, *45*, 5260.
6. Sayyed, I. A.; Sudalai, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3111.
7. (a) George, S.; Narina, S. V.; Sudalai, A. *Tetrahedron* **2006**, *62*, 10202; (b) Kotkar, S. P.; Sudalai, A. *Tetrahedron: Asymmetry* **2006**, *17*, 1738; (c) Narina, S. V.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 6799; (d) Kotkar, S. P.; Sudalai, A. *Tetrahedron Lett.* **2006**, *47*, 6813; (e) Narina, S. V.; Talluri, S. K.; George, S.; Sudalai, A. *Tetrahedron Lett.* **2007**, *48*, 65.
8. (a) List, B.; Seayad, J. *Org. Biomol. Chem.* **2005**, *3*, 719; (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138; (c) Houk, K. N., List, B., Eds.; *Acc. Chem. Res.* **2004**, *37*, 487; (d) List, B., Ed.; *Adv. Synth. Catal.* **2004**, *346*, 1021; (e) Bolm, C., Ed.; *Adv. Synth. Catal.* **2004**, *346*, 1022; (f) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
9. For a review of proline-catalyzed asymmetric reactions, see: List, B. *Tetrahedron* **2002**, *58*, 5573.
10. (a) Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293; (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247; (c) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2003**, *43*, 1112; (d) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808; (e) Cordova, A.; Sunden, H.; Bøgevig, A.; Johansson, M.; Himo, F. *Chem.—Eur. J.* **2004**, *10*, 3673.
11. (a) List, B. *J. Am. Chem. Soc.* **2002**, *125*, 5656; (b) Bogevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790; (c) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254; (d) Vogt, H.; Vanderheiden, S.; Brase, S. *Chem. Commun.* **2003**, 2448; (e) Iwamura, H.;

Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 11770.
12. *The Merck Index: An Encyclopedia of Chemicals, Drugs and Biologicals*, 13th ed.; Merck: Whitehouse Station, NJ, 2001.
13. *Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: New York, NY, 1982; Vol. 1.
14. Sone, H.; Shibata, T.; Fujita, T.; Ojika, M.; Yamada, K. *J. Am. Chem. Soc.* **1996**, *118*, 1874.
15. Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *54*, 1295.
16. Nakamura, K.; Kawasaki, M.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1079.